Evaluation of the Urea Washout Pyelogram and Urography in the Assessment of Renovascular Hypertension

D. C. F. HARWOOD-NASH, M.B., Ch.B., D.M.R.* and
E. L. LANSDOWN, M.D., F.R.C.P.[C],† Toronto

The urea washout (UWT) modification of the intravenous pyelogram was used to study 146 hypertensive patients in order to detect the presence of significant renovascular abnormalities. A positive result was obtained in 55 patients and direct confirmation of main renal artery stenoses by selective renal arteriography was obtained in 26. Bilateral abnormalities were confirmed in seven of the 26 patients. No false-negative results were encountered. The usefulness of this test as a comprehensive screening test is outlined. It demonstrated a high degree of accuracy in the diagnosis of significant unilateral or bilateral main renal artery stenosis in addition to the detection of diffuse intrarenal arteriolar disease. It was of value in the postoperative assessment of operative repair of main renal artery defects. The urea washout test embodies both an anatomical and a physiological approach in the roentgen diagnosis of curable renovascular hypertension. The altered physiology resulting from significant main renal artery stenosis makes possible the use of the urea washout intravenous pyelogram. The value of other forms of intravenous pyelography is described.

La méthode de pyélographie intraveineuse avec diurèse provoquée a été utilisée pour examiner 146 hypertendus, en vue de déceler la présence éventuelle d'anomalies rénovasculaires notables. On a obtenu un résultat positif chez 55 malades et, dans 26 cas, il a été possible de confirmer directement une sténose de l'artère rénale principale par une artériographie rénale sélective. Sept de ces 26 malades présentaient des anomalies bilatérales confirmées. On n'a pas noté de résultats faussement négatifs. Les auteurs soulignent l'utilité de ce test, comme épreuve de dépistage, en ce qu'il a permis de porter un diagnostic très précis de sténose unilatérale ou bilatérale de l'artère rénale principale et, en outre, de découvrir la maladie artériolaire intrarénale diffuse. Ce test s'est révélé précieux comme moyen d'évaluation post-opératoire des reconstructions chirurgicales des vices de l'artère rénale. Le test de pyélographie avec diurèse provoquée constitue un moyen de diagnostic radiologique qui fait appel à la fois à l'anatomie et à la physiologie et qui est utile pour dépister les cas curables d'hypertension rénovasculaire.

HYPERTENSION, multifactorial in origin, a "mosaic",[32] is a clinical manifestation of a pathological process. The historical correlation of hypertension and renal disease[47] in 1827 has evolved to establish the concept of an ischemic renovascular lesion causing systemic hypertension.[3, 14, 16, 34, 35, 45] This concept includes the principle that hypertension so produced can be reversed by removal of significant renal arterial constriction or of the affected kidney. Curable hypertension due to renovascular disease is an established entity.

It is the purpose of this paper to discuss the utilization of the specific physiological changes produced in the kidney by renovascular lesions in the assessment of hypertension by radiological methods, namely the urea washout modification of the intravenous pyelogram, and to correlate the results of this investigation with the objective findings of arteriography, surgery and pathology.

Approximately 3% of the adult population of the United States have hypertension and 2 to 25% (10%) of these hypertensives will have a demonstrable cause; the majority are renovascular in origin.[54] Recent studies have shown, however, that renal artery stenosis per se as demonstrated by necropsy or angiography does not necessarily indicate hypertension. Eyler[12] found

that 32% of his normotensive patients had some type of renal artery disease while the incidence of renal artery pathology in hypertensives referred to clinics approximated 25% of patients.[9, 29, 36]

Renal artery stenosis, therefore, must be of sufficient severity to cause a significant alteration in the hemodynamics of the vessel distal to the stenosis. In hypertension of renovascular origin, the release of renin and the ultimate formation of the pressor substance angiotensin II establish the two main theories of the pathogenesis of hypertension due to significant renal stenosis: (1) impaired blood flow (effective renal plasma flow) to functioning renal tissue resulting in ischemia,[21] and (2) a decreased pulsation in renal tissue as a result of the arterial stenosis or scarring.[23]

The resultant effects[5] of these two hemodynamic changes are alterations in the stretch effect of afferent arterioles and in renal arterial pulse pressure and mean arterial pressure. Renal volume pulsation and a pressure differential between afferent arterioles and the distal tubule are similarly altered.

Small renal arterial disease (arteriolar nephrosclerosis) results in similar and possibly more severe hemodynamic alterations than found in main stem renal arterial stenosis, but at present is not curable. Resistance in a cylinder is inversely proportional to the fourth power of the radius; thus a relatively minute decrease in size of the small vessels results in a disproportionate increase in resistance and hence a decrease in pressure distally.

It has been deduced experimentally[6] that at least 50-60% constriction of the main renal arterial lumen is needed to significantly decrease the pulse pressure and blood flow to the involved kidney in order to initiate the renin-angiotensin mechanism. Measurement of the pressure gradient across the stenotic lesion is a more accurate method of assessment and although small gradients may at times be significant, it is generally agreed that the gradient in curable disease is usually in excess of 40 mm. Hg.

Stamey et al.[43] emphasize that marked obstruction to renal blood flow is needed before the renal plasma flow to the kidney as measured by the clearance of para-aminohippuric aminohippuric acid (C_{pah}) is affected. He found that a reduction of at least 37% in renal plasma flow relative to the normal kidney was necessary before it was significant. He also postulated that if the (C_{pah}) was not affected, irrespective of the anatomical lesion, hypertension did not result. Selkurt[38] has shown in dog experiments that the mean arterial blood pressure can be dropped

from 160 to 100 mm. Hg without any change in the (C_{pah}) or glomerular filtration rate.

Morris et al.[29] state, however, that gradients have no relation to clinical responses, and found gradients less than 25 mm. Hg in 25% of their patients with correctable renovascular lesions.

PHYSIOLOGICAL ALTERATIONS IN THE NEPHRON

The physical alteration, namely reduction in renal blood flow, has been discussed. This is believed to be the primary cause of the reduced glomerular filtration rate and the hypertension.[43]

The most invariable characteristic of renal ischemia is excessive reabsorption of water and sodium by the tubules. The occlusive arterial disease results in a reduced renal plasma flow (RPF). This in turn decreases the glomerular filtration rate (GFR). The tubules, however, continue to reabsorb sodium and water at a normal or greater rate, and with a decreased urine flow as a result of the decreased GFR, relatively more sodium and water are reabsorbed. This occurs predominantly in the proximal tubule, where the sodium remains equimolar with plasma. The increased sodium reabsorption results essentially in the excessive water reabsorption on an osmotic basis.

Howard et al.[20] reported four patients with hypertension due to unilateral renal disease, all of whom showed a reduction in the rate of urine excretion from one kidney of more than 50% relative to the normal kidney, in addition to a 15% or more reduction in sodium concentration on the affected side. Rapoport[37] modified the resultant "Howard" test by utilizing creatinine concentration measurements. Stamey et al.[43] further modified the test by measuring inulin concentration in the urine. It is significant to note that these estimations necessitate catheterizations of the respective ureters. Resultant spasm and edema of the ureters have been reported,[21] with consequent modification of results. Inulin is excreted entirely by glomerular filtration, as are iothalamates and the diatrizoate compounds used as the contrast medium in the urea washout test (UWT). Stamey[43] has shown that in renovascular ischemia the affected kidney concentrates inulin by at least 100%. The diatrizoates are thus similarly concentrated in the tubules and collecting system.

Levinsky, Davidson and Berliner[25] and later Stamey and his associates[48] utilized urea to amplify the differences in water absorption which are further exaggerated if the GFR is reduced by renal artery stenosis.

When a potent diuretic such as urea is infused it accentuates the difference in urine excretion be-

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tween the normal and the ischemic kidney. Furthermore, as more and more sodium reabsorption occurs along the renal tubules, urea, an osmotic diuretic, constitutes a progressively greater proportion of the total osmotic pressure of the tubular urine. Passive reabsorption of the urea occurs and additional water is reabsorbed. This phenomenon is more marked in the ischemic kidney, owing to the slower GFR and possibly the altered dynamics of the ischemic tubular wall. On the other hand, mannitol, often used as the diuretic in this form of examination, is not reabsorbed through ischemic tubules, and this retention of mannitol in the damaged tubules decreases the relative difference in tubular fluid volume between the normal and abnormal nephrons, as it retards water and sodium reabsorption.[43] Thus urea infusion provides an adequate urine flow rate and creates conditions for demonstration of maximum disparity in studies of differential renal ischemia.

Amplatz[1] in 1962 applied these physiological principles to the intravenous injection of diatrizoate compounds followed by an infusion of urea-saline to provide an objective radiographic assessment of renovascular hypertension, based on a functional abnormality rather than on the demonstration of only an anatomical vascular stenosis or defect.

MODIFICATIONS OF THE INTRAVENOUS UROGRAM

1. Simple Intravenous Urogram

In recent years sophisticated variations of the basic theme of the intravenous urogram have rapidly matured. Gross renal changes are necessary before a significant alteration in the routine urogram occurs. The intravenous urogram is indispensable in the assessment of obstructive uropathy and mechanical defects, such as tumours, cysts and ureteral abnormalities. Although reported studies[50] state that the simple excretory urogram suggests the presence of renovascular disease, many centres have not found this method alone to be accurate.

Renal size as a reflection of renovascular disease has been extensively studied, and it has been found that this factor reflects only severe disease and cannot be applied with any certainty towards a positive diagnosis of renovascular abnormalities in the early stages of this disease. The statistical basis for the correlation between renovascular disease and kidney length has been reported by a number of workers.[10, 17, 88] Don,[11] however, made the important point that it is the correlation of renal length and the renal parenchymal thickness that is important in the assessment of renovascular disease.

Renal size differential is indeed a reflection of renovascular disease at certain stages of the process itself, but before this late stage is attained the differential may not be apparent. A difference in renal size supports a positive diagnosis; however, if there is no difference, renovascular hypertension is not excluded.

In 100 intravenous urograms North and Derrick[31] made correct predictions of hypertension in 43%, but erroneous predictions in 38%. Morris et al.[29] reported a 30% false negative assessment in patients subsequently proved to have renovascular occlusions, while Winter[53] reported only a 65% accurate correlation. Dustan and Page[9] reported that 72% of 128 patients with confirmed renal artery stenosis had faulty urograms.

It is apparent that further modifications to the simple intravenous urogram are necessary in order to assess the functional aspect of renovascular disease in hypertension.

2. Rapid Sequence Urogram

The first modification to the simple urogram was a series of films taken for five minutes at one-minute intervals, following a rapid intravenous injection of contrast medium. Discrepancy in the appearance of contrast medium, intensity of contrast medium and difference in length were noted.

Although usually reliable results were obtained by this method, changes were often very subtle and were indeed often seen only in retrospect. A unilateral renal stenotic lesion should produce a delay in nephrogram appearance, a delay in appearance of contrast medium of at least one minute and a hyperconcentration of dye in the pelvicalyceal system. These changes are dependent on the diminished perfusion, a reduced rate of urinary output and an excess in reabsorption of water, respectively.

Martin, Deyton and Glenn,[26] Maxwell et al.[27] and Amplatz[1] have reported their findings after using this modified technique. Maxwell et al.[27] noted that of 42 patients with renovascular hypertension, 39 showed abnormalities in a rapid-sequence urogram, discrepancy in appearance time of contrast medium being the most frequently seen abnormality. Amplatz, however, was of the opinion that this modification alone, although valuable, was still not completely satisfactory in all cases of renovascular hypertension, particularly bilateral lesions. Wilson et al.[51] reported that increased concentrations of contrast medium in the renal collecting systems were present in only six of 128 patients, using the rapid-sequence method alone.

3. Urea Washout Modification of the Intravenous Urogram

Amplatz[1, 2, 44] has shown that with a decreased GFR relatively more water is absorbed, resulting in hyperconcentration of contrast media in the ischemic kidney. Less contrast medium is present, however, than in the normal kidney. Relatively less reabsorption of water occurs in the tubules of the normal kidney, but more contrast medium is present in the glomerular filtrates of the latter, owing to a greater renal plasma flow. In a short period of time, as in the rapid-sequence urogram, the concentrations may not be significantly different. Furthermore, differences in concentration were only noted in lower dilutions.[2]

The difference in urine flow and hyperconcentration of contrast medium between the normal and ischemic kidney can be remarkably enhanced by a sudden diuresis during intravenous urography following adequate filling of both collecting systems by contrast medium. Initially the water load diuresis was utilized by Brown et al.,[4] but Amplatz and his co-workers[1] and Stamey et al.[43] found urea to be a more efficient diuretic.

Thus, because of the altered physiology of the nephron resulting from renovascular disease, it is possible to obtain objective radiographic evidence of the disease by the infusion of a potent diuretic, urea. Such an infusion magnifies the relative discrepancy of the concentration of contrast medium in the pelvicalyceal system, resulting from the altered physiology.

The unilateral decrease in urinary output is manifested radiographically by a slower passage of urine through the nephron into the pelvicalyceal system, and is cleared by pelvic peristalsis, which is unchanged. This clearance is delayed, however, by the decreased urine flow from the nephrons and collecting tubules themselves.

The urea washout test incorporates both the rapid-sequence pyelogram and osmotic diuresis. Its purpose is to delineate accurately and radiographically both the morphological abnormalities and the altered physiological sequelae of renovascular disease. In essence it combines an intravenous rapid-sequence urogram and a "radiographic" Howard test!

CONTRAINDICATIONS

The test is contraindicated in patients with heart failure, severely impaired renal function and recent myocardial infarction. Patients on a low salt diet or those taking diuretics should not have the test. If the patient has had an intravenous pyelogram and poor concentration of the dye is seen on the 12-minute film, the urea washout test is contraindicated. Iodine sensitivity precludes the test.

METHOD OF STUDY

The entire test took about one hour from the time a radiograph of the abdomen ("scout" film) was first taken with the patient lying supine on the table. Abdominal binding was not used. Intravenous infusion was established by percutaneous venipuncture of an arm vein with a No. 18 needle, connected by tubing to the main stem of a Y-tube intravenous set. One tube of the Y was connected to a bottle containing 500 c.c. of 5% glucose-water; the other to a bottle containing 500 c.c. of normal saline in which 40 g. of urea* had been dissolved. A 2-ml. test dose of Hypaque-75% was given through the tubing, followed two minutes later by a rapid injection of 50 c.c. of Hypaque-75%. Films were taken at 30 seconds, two, three, five, eight and 12 minutes. If an intravenous pyelogram had not previously been done, films at eight and 12 minutes were of the 14 x 17 inch size; otherwise 10 x 12 inch films were used. The gonads were shielded during all exposures.

The urea-saline infusion was begun immediately after the 12-minute film and run in over a period of 15 minutes. Additional films were taken every three minutes until at least 30 minutes had elapsed after the start of the urea in saline. Again, if there had been no previous IVP, bladder radiographs, both pre- and post-voiding exposures, were taken. The patient was hydrated with the 500 c.c. of glucose-water; oral fluids were also given. When headache occurred, codeine grain ½ was given orally.

The time of appearance of the contrast medium in the collecting system was noted on each side and the length of each kidney was measured. The difference in density of the contrast media, if any, was assessed before the urea infusion was given.

A simultaneous bilateral dilution and washout of contrast medium within 25-30 minutes after the urea infusion is started constituted a normal test. It is important to note that it must be a significant, prompt and bilateral dilution. Some residual contrast medium may still be present 30 minutes after the start of the urea infusion but at a markedly lower dilution. This finding is normal. A bilateral normal washout phase is shown in Fig. 1a, b and c.

POSITIVE CRITERIA

Few cases possessed all the points detailed below. The ultimate factor in the diagnosis of
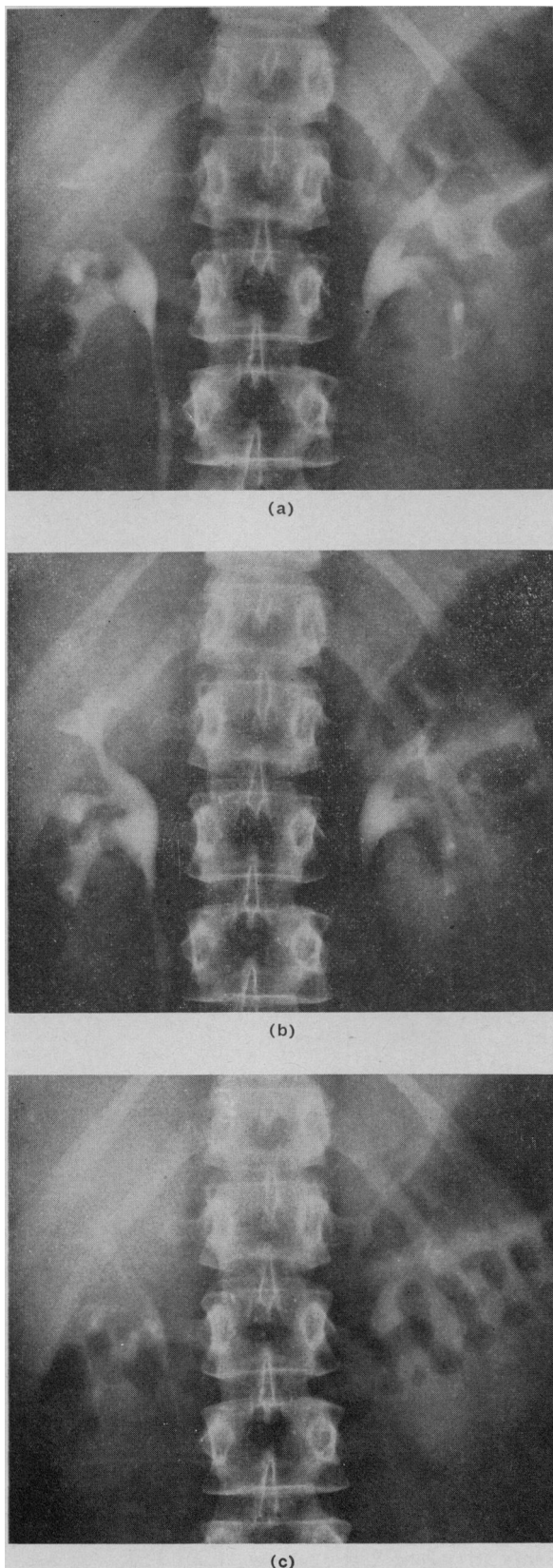
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*Ureaphil-Abbott.

Fig. 1.—A normal UWT: (a) Equal opacification at 12 minutes and at start of urea infusion. (b) No washout at three minutes after infusion. (c) Equal and bilateral washout at nine minutes after infusion.
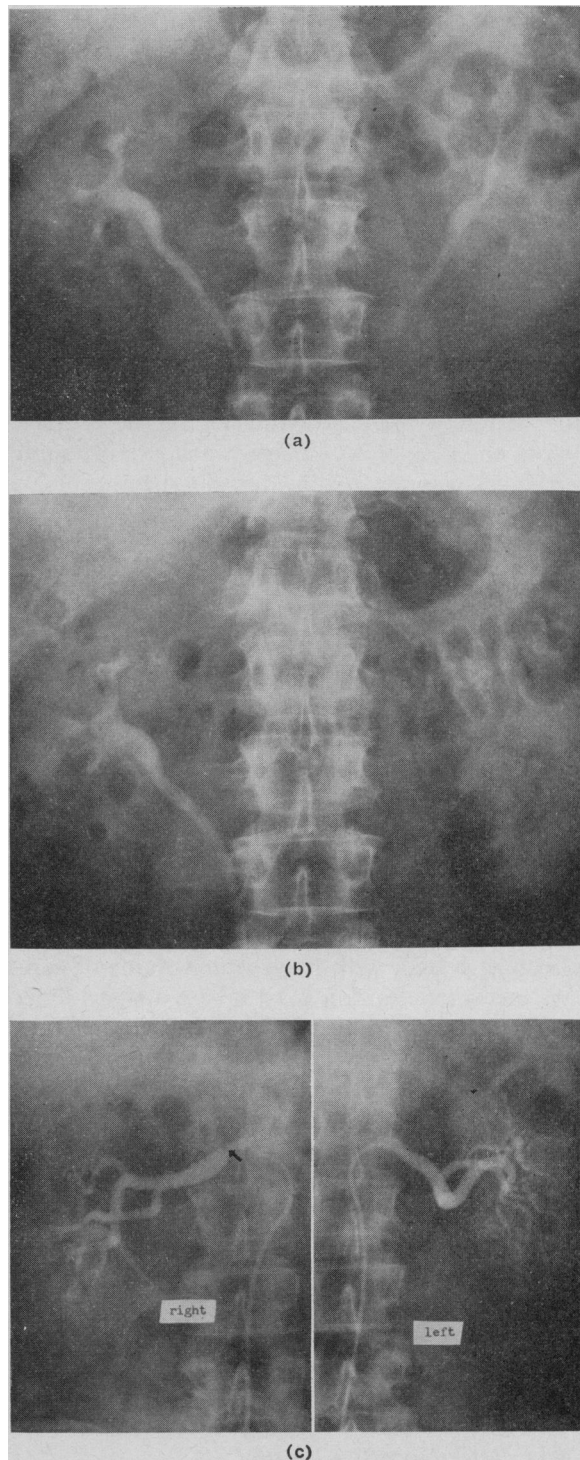

Fig. 2.—A unilateral positive UWT on the right: (a) Hyperconcentration on right at 12 minutes and at start of urea infusion. (b) Retention of contrast medium on right with complete washout on left nine minutes after the start of the urea infusion. (c) Right main renal artery stenosis with a normal left renal artery. Note that both kidneys are of equal length. Repair of the stenosis resulted in a marked drop in blood pressure postoperatively.

renovascular disease was a significant unilateral or bilateral delay in washout.

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(a) *Positive Test — Unilateral (Fig. 2)*

The observations which constitute a positive unilateral UWT[1, 2, 39, 44] were a delay in appearance of contrast medium; a less dense nephrogram in the abnormal kidney initially, and then on the same side an early hyperconcentration of contrast material more dense than the normal side; a decrease in size of the affected kidney greater than 1.5 cm. A delay in washout of contrast medium in the collecting system of the abnormal kidney of six to nine minutes subsequent to a washout on the normal side constituted the major criterion for a positive assessment. The other criteria were used either as complementary factors or in cases in which a washout, although suspected, was not within the stated limits.

(b) *Positive Test — Bilateral*

A bilateral positive result was a retention of contrast medium in both collecting systems with no significant washout 30 minutes after the start of the urea infusion (Fig. 6). A trace of contrast medium was often seen at that period but a definite dilution had occurred, and these cases were considered to be negative.

(c) *Pseudo-Positive Washout (Fig. 3)*

An equivocal result may be due to a number of renal abnormalities other than renovascular stenosis—a pseudo-positive washout. In a larger collecting system with its greater volume of contrast medium, dilution may take a longer time. In addition, an increased density of the collecting system due to overlying gas patterns, renal pelvic peristalsis or renal disease such as pyelonephritis provides a false appearance of unilateral hyperconcentration. Malrotation, on the other hand, may present a greater thickness of contrast medium, and thus the medium may appear more dense than the other side. A ureteropelvic or ureteral block, or edema due to a calculus, edema secondary to a stone or previous catheterization or extrinsic pressure from an aberrant vessel, may all cause a delay in emptying.

(d) *False-Negative Results*

Failure to detect segmental renal artery stenosis (whether of a single renal artery radical or an accessory renal artery) constituted the main disadvantage of the urea washout test. The bulk of normal functioning kidney tissue may mask the physiological abnormalities produced by such a segmental lesion, and yet this also may produce hypertension.
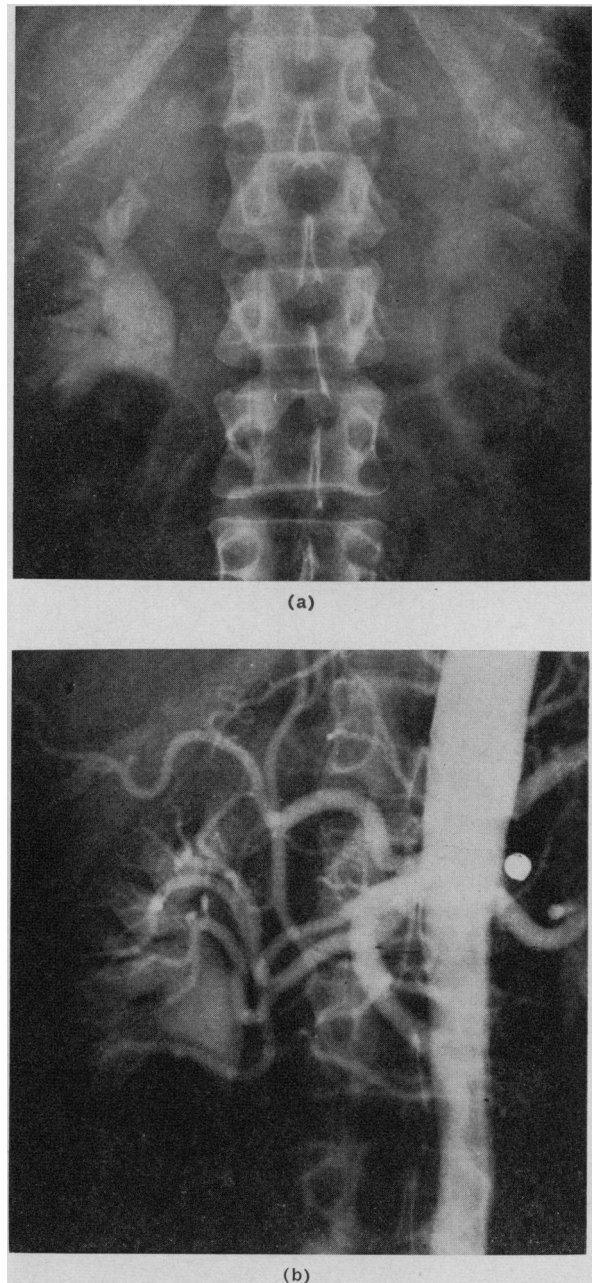

Fig. 3.—A pseudo-positive UWT: (a) Delay of washout on right side. (b) An accessory renal artery causing an apparent obstruction at uretero-pelvic function.

RESULTS

One hundred and forty-six patients were subjected to the UWT over a period of 14 months in the Department of Radiology, Toronto General Hospital. Hypertension was the common presenting diagnosis. The tests were performed as a prospective assessment in all but three patients in whom the urea washout test was performed after aortography to assess the physiological effects of a stenotic lesion.

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1. Age and Sex

The series was comprised of 64 women and 82 men, with an age span of 29 to 70 years, 61% of whom were under the age of 55.

2. Positive Results (Table I)

Fifty-five (37.6%) of the 146 patients were found to have positive UWT of which 35 were unilaterally positive and 20 bilaterally positive. Fifty-seven patients had arteriographic examination, which in most instances included selective renal arteriography in addition to aortography. Twenty-eight of the 35 unilateral positive patients underwent arteriography and 19 of these were shown to have significant main renal artery disease. Nine cases had no demonstrable abnormality and were designated pseudo-positives. In a *pseudo-positive* assessment some factor other than renovascular was therefore present. Eleven of the patients with the bilateral positive UWT underwent arteriography, and seven of these showed renal artery disease. Three cases were designated pseudo-positives and one a false-positive. A *false-positive* assessment is one in which no renovascular or extraneous cause can be found to account for the positive urea washout test. It must be noted, however, that in two of the bilateral positive cases unilateral renal artery stenosis was demonstrated. In one unilateral positive UWT, a bilateral renal artery stenosis was demonstrated (Case 1).

Three of the four patients with segmental stenoses had main artery stenosis on the same side as well. One of the bilateral positive cases showed no main or segmental stenosis but the small artery pattern was that of arteriolar nephrosclerosis on arteriography.

Of the 39 patients in whom arteriography was performed, four were found to have fibromuscular hyperplasia; all of these were women. All of these patients had a unilateral positive UWT (Fig. 4). One subject had a diffuse abdominal aortic aneurysm with a bilateral positive UWT. An interesting finding was that 17.5% of the cases examined by arteriography had one or more accessory renal arteries.

RADIOGRAPHIC MANIFESTATIONS OF 55 POSITIVE UREA WASHOUT TESTS

All of the cases showed delay in washout, either unilateral or bilateral. Twenty-five (71.5%) of the 35 unilateral positives showed hyperconcentration and a positive washout after the start of the urea infusion (Fig. 2) while nine (25.7%) showed only a slight delay in the nephrogram and a positive delay in washout. Four patients (14.3%) had a delay in the nephrogram and in washout, and hyperconcentration as well.

Five of the 19 unilateral positive subjects (26.3%) who were confirmed by arteriography exhibited a decrease in kidney size of more than 1.5 cm. relative to the contralateral normal kidney. Eleven (58%) of the 19 patients exhibited a decrease in kidney size of less than 1 cm. (in seven of these 11 subjects the right side was affected), while in three (15.8%) the length was *greater* than the normal kidney. Three (4.9%) of the 62 patients with negative UWT in which accurate measurements were possible showed one kidney more than 1.5 cm. smaller than the other. Of these three, one was a right-sided kidney.
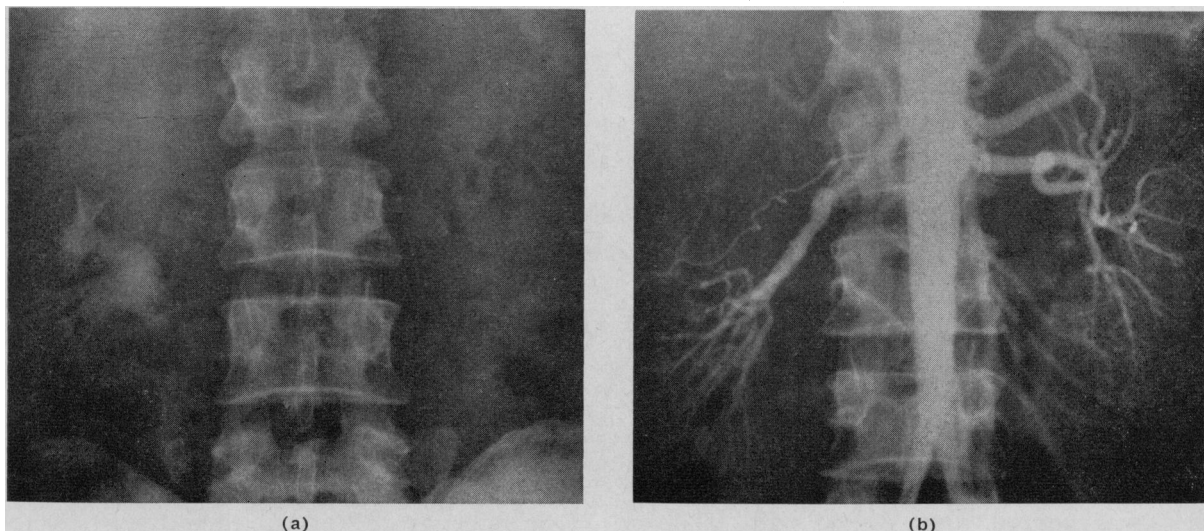

Fig. 4.—A unilateral positive UWT due to fibromuscular hyperplasia of right renal artery:
(a) Delay in washout on right side. (b) Fibromuscular hyperplasia of right renal artery.

PSEUDO-POSITIVE RESULTS

Twelve cases were assessed as "pseudo-positive"—nine unilateral and three bilateral. One bilateral positive was considered to be a false positive.

Of the nine unilateral pseudo-positive cases three had accessory renal arteries crossing near the pelviureteral position causing a relative obstruction to pelvic emptying (Fig. 3). Two cases were reviewed and found to have evidence of pyelonephritis. These cases of pyelonephritis are termed pseudo-positive owing to the irregularity and local deformity of the collecting system which may in itself appear more dense and cause delay in the clearance of contrast medium. One case had a slow clearance of contrast medium from the small arteries during arteriography suggestive of small artery disease, and two cases had unilaterally dilated pelves with a relatively greater density of contrast medium. In the remaining case the UWT was performed after a bout of flank pain, and possibly the resultant spasm or edema of the collecting system produced the delay.

Of the three bilateral pseudo-positive examinations one case had bilateral pyelonephritis; one examination was performed the day following a Howard test and again spasm may have been present. One case had toxemia of pregnancy. Here one might consider a hemodynamic abnormality as being present and initiating the hypertension.

Only one case could not be accounted for and must be termed a false positive. It is acknowledged, however, that diffuse small renal vessel disease may be associated with pyelonephritis and in itself initiate renovascular hypertension.

NEGATIVE TESTS

Ninety-one tests (62.4%) were negative. Eighteen of the 91 negative cases were confirmed by arteriography. Thus in about 20% of cases checked, no false negative cases were detected. Owing to circumstances beyond our control, arteriography was not performed on the remaining patients.

MISCELLANEOUS

There was no specific relationship between the variation in length of the affected kidney after infusion compared with the variation in length of the normal kidney. There was an increase in length ranging from 0.1 cm. to 1.3 cm.; this increase was usually symmetrical and no specific difference between the normal and abnormal side was noticed. One patient with bilateral positive UWT was hypertensive after toxemia

of pregnancy. Her blood pressure subsequently returned to normal. A repeat UWT was not done. One patient with bilateral positive UWT had systemic lupus erythematosis (Case 2). One patient presented with hyperaldosteronism and was found to have a negative UWT.

DISCUSSION

This study was designed to evaluate the usefulness of the UWT in the screening and assessment of hypertensive patients, in order to detect renovascular disease as the probable etiological agent.

Whenever possible, UWT was compared with a renal arteriogram and in one case autopsy material was reviewed.

Selectivity of the patients screened by this test could be less restrictive. It would be necessary to screen all those with hypertension who are young, female, and have no family history of this condition; in whom the hypertension is of recent onset or is difficult to control by a medical regimen; or who have any of the following: flank pain, hematuria, epigastric bruits or hypokalemia.

(a) Comparative Series

Table I shows that this series has a relatively large percentage of true positives—that is, cases confirmed by arteriography (17.8%). In addition, seven with proved bilateral positive results in this series form a significant group which demands further study.

TABLE I.—RESULTS OF THE UREA WASHOUT TEST

	Unilateral	Bilateral	
Total cases			146
Total positive (UWT)	35	20	55 (37.6%)
Confirmed positive (with arteriogram)	19	7	26 (17.8%)
Pseudo-positive (with arteriogram)	9	3	12
False positive (with arteriogram)	—	1	1
Total normal			91 (62.4%)
Confirmed normal (with arteriogram)			18
False negative			0

The comparative series in which detailed findings have been reported are by Stejskal et al.,[44] Schreiber et al.[39] and Witten et al.[55]

Amplatz and his associates reported that of 463 hypertensive patients, 15 (3.24%) had positive UWTs; 14 with significant renal arterial stenosis and one false positive. Seventeen cases were assessed as pseudo-positives.

Schreiber et al.[40] in a retrospective study report that of 50 hypertensive patients who under-
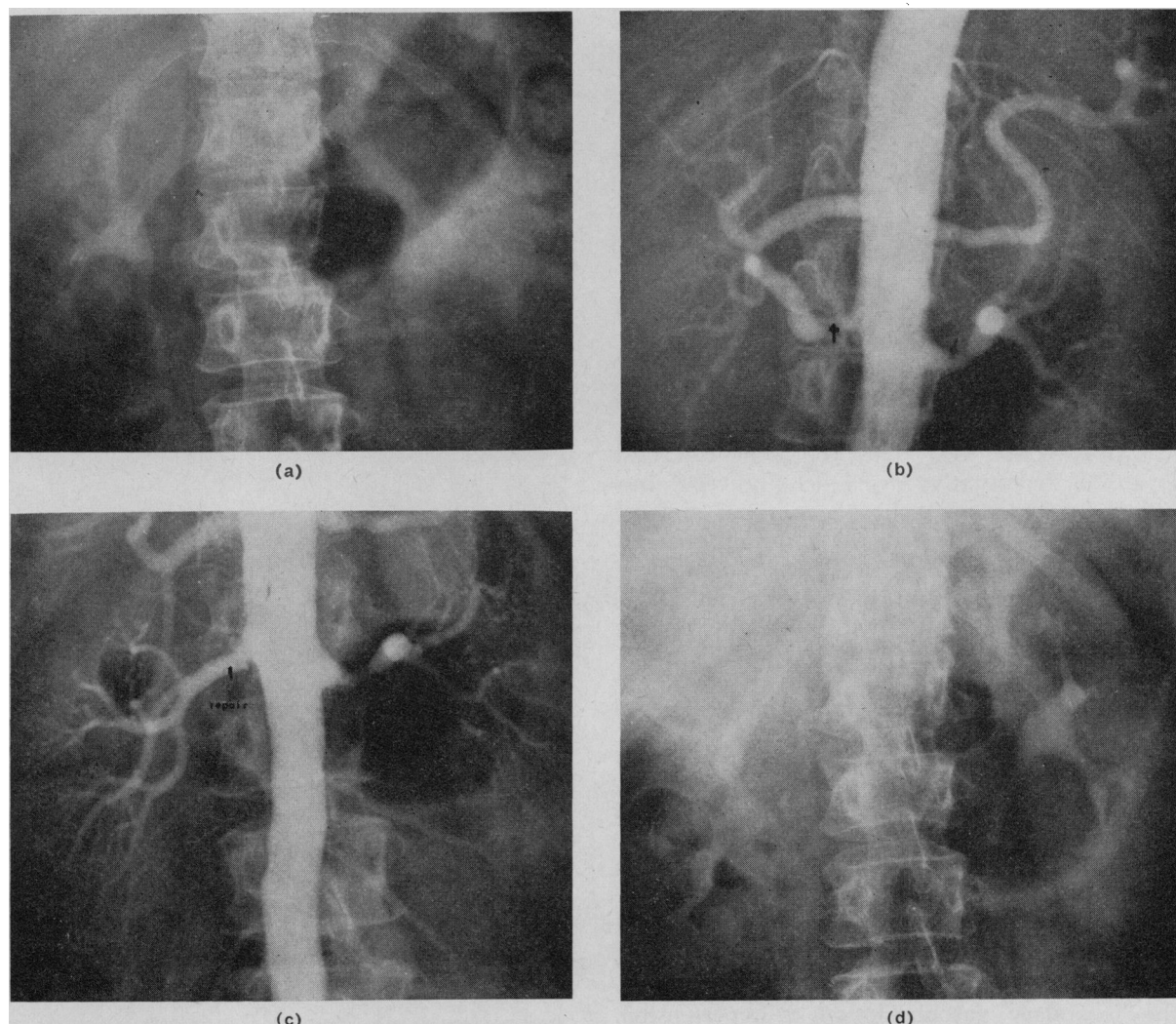
Fig. 5.—Case 1 with a unilateral right-sided positive UWT with bilateral renal artery stenosis: (a) A right-sided positive UWT. (b) Bilateral main renal artery stenoses. (c) Post-operative right renal artery with repair of the stenosis. Blood pressure dropped to near normal. (d) Left-sided positive UWT one year after operation with recurrence of hypertension.

went UWT, 10 were positive. Two of these positive results were found on the same patient preoperatively and postoperatively; one patient had no arteriography but the subsequent renal biopsy showed evidence of pyelonephritis and arteriolar nephrosclerosis, and in one case the arteriography was inadequate. There was one false positive in that the arteriography was inconclusive and a repeat UWT was negative. This latter cannot be counted as a positive, nor can the postoperative UWT referred to above really be included. It is also noted with some interest that the postoperative UWT in Schreiber's Case I was positive when the patient's hypertension recurred and that nephrectomy resulted in marked improvement.

Witten et al.,[55] utilizing a mannitol washout test in both "primary hypertensive" and reno-vascular hypertensive subjects, report positive results in 13 of the 32 patients studied. Eleven of 16 patients with renovascular hypertension were positive and of these 11, three were classed as false positives. In addition, five false negative results were reported.

Schreiber et al.[40] in a later report studied 33 normotensive volunteers and stated that eight of the 33 studies revealed "bilateral retention of contrast medium in a concentration sufficient to allow visualization even on films exposed as late as 27 to 35 minutes following the start of the urea infusion". This phenomenon has been noted in this series, but we feel that sufficient washout occurred in the majority of cases classed as negative before the 30-minute postdiuretic film. In some cases the contrast medium washout was complete only to return in a faint opacification of the renal pelvis in the later films! These were also classed as negative.

Amplatz makes no reference to relative disparity in renal length whereas Schreiber found three of 10 cases to have a decrease in length of more than 1 cm. Similarly we have found that renal length is of relatively little value in the overall assessment of significant renovascular disease. ·

Two investigators[39, 44] found that there was excellent correlation between split function tests and the urea washout result. In the present series similar correlations were found. Split function tests, however, are viewed with some disfavour in many centres.[13, 22, 44] Morbidity, technical difficulties and laboratory errors may occur even in the most experienced hands.[15, 44, 51] However, a split function test does represent the best means of quantitative assessment of renal disorders but is thought by the authors and by others[39] to be inadequate in terms of bilateral renovascular disease, as it relies essentially on the comparison of the sides whereas the UWT is an objective test for both sides individually and simultaneously.

(b) Incidental Renal Artery Stenosis

Incidental renal artery stenosis—that is, a functionally insignificant stenosis—is not uncommon. It has been shown to occur in patients with unilateral stenosis in whom negative split function tests and negative UWT are present.[2] An interesting facet of renovascular hypertension in animals is a report by Wilson and Byrom,[52] who observed that a kidney supplied by a stenotic renal artery was "protected" from the "secondary" vascular lesions of hypertension. These authors state that the kidney on the side of the arterial occlusion is potentially the healthier one and should, therefore, be preserved.

The following case illustrates three important facets, namely an inconsequential renal stenosis, successful renal artery reconstruction at operation, and the progression of renal vascular disease with the return of hypertension demonstrated by the urea washout test.

CASE 1.—H.H., female, aged 52 (Fig. 5).—This 52-year-old woman had a history of hypertension and dizzy spells for seven years with no improvement on medication. Her blood pressure on admission was 210/110 mm. Hg. No epigastric vascular bruit was present.

The UWT demonstrated a right-sided positive result (Fig. 5a). The right kidney was 2.2 cm. smaller than the left. Split function tests confirmed the abnormality. Arteriography showed bilateral renal artery stenosis (Fig. 5b). A right renal arterioplasty was performed. A postoperative arteriogram showed a right non-stenotic vessel (Fig.

5c). The patient's blood pressure fell to 160/90 mm. Hg. The right kidney had increased in length by 0.3 cm. and was now only 1.2 cm. shorter than the left, the left having decreased by 0.9 cm.

Thirteen months later her blood pressure had risen to 180/100 mm. Hg and a repeat UWT was now negative on the right side but positive on the left (Fig. 5d). An arteriogram now showed slight narrowing of the right anastomosis and the previously noted left-sided stenosis.

By inference, therefore, the left kidney was now the origin of her hypertension. At present her blood pressure is over 200/100 mm. Hg. The simple
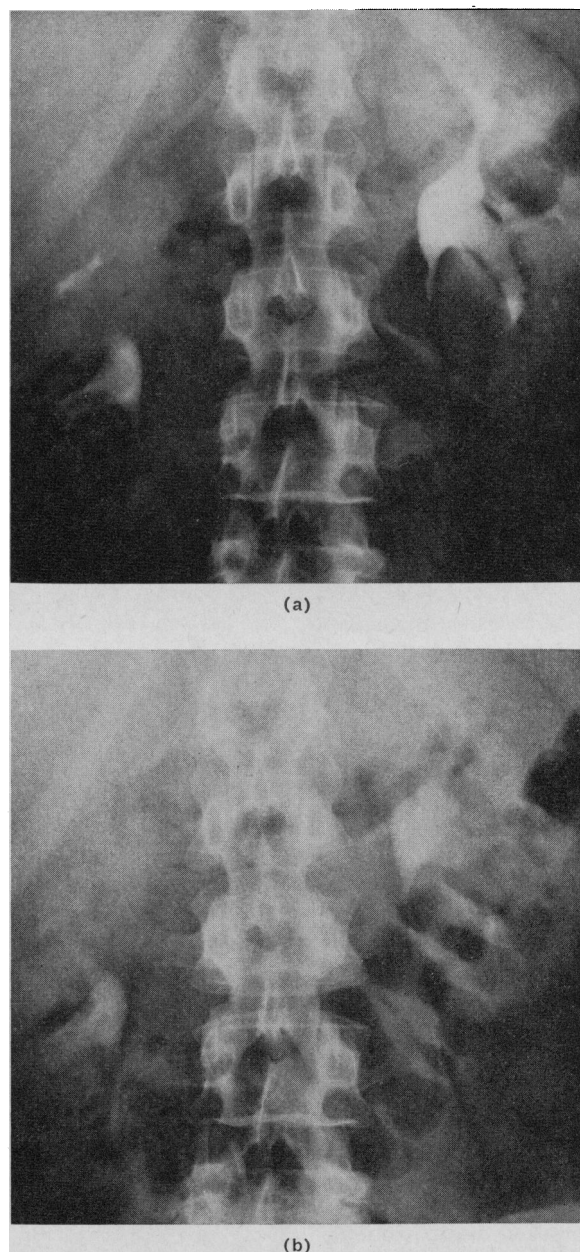

(a)

(b)

Fig. 6.—Bilateral positive UWT: (a) Radiograph taken at start of the urea infusion. (b) Lack of washout bilaterally at 42 minutes after start of urea infusion. This patient with clinical lupus erythematosus was found at necropsy to have severe atrial nephrosclerosis.

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reassessment of this case by UWT provided the clue to the pathogenesis of this patient's progressive and recurrent hypertension.

(c) Intrarenal Arterial Disease—Positive Bilateral

A second case illustrates the diagnostic accuracy of the UWT in bilateral small renal vessel disease associated with hypertension.

CASE 2.—E.McA., female, aged 30 (Fig. 6).—This patient was admitted with "possible" acute hypertensive encephalopathy. Clinically the patient had systemic lupus erythematosus. Her blood pressure on admission was 160/120 mm. Hg. LE cells were demonstrated on several occasions. UWT was bilaterally positive (Fig. 6). The patient died within five months of UWT, and autopsy showed diffuse arterial nephrosclerosis with typical hyalinization of the arterioles and capillaries compatible with disseminated lupus erythematosus.

The UWT demonstrated significant bilateral intrarenal vascular disease and this suggested the need for bilateral renal biopsies.

Goldblatt[15] recently made a strong statement that diffuse intrarenal obliterative vascular disease should be considered just as effective as main artery stenosis in the initiation of the renin-angiotensin system as described. Is it the arteriolar nephrosclerosis that initiated the hypertension or is it the hypertension that caused arteriolar sclerosis in the kidney and elsewhere? These questions as yet have not been conclusively answered. However, the assessment of arteriolar or arterial nephrosclerosis by the UWT from whatever cause, be it idiopathic, scleroderma, disseminated lupus erythematosus, amyloid, periarteritis nodosa, diabetes, toxemia of pregnancy, etc., is essential if one is to attempt to unravel the problem as posed above.

Meany et al.[28] in a study of both normal and hypertensive patients, using in vitro arteriography and pathological examination of kidneys removed from normal and hypertensive patients, found that kidneys from hypertensive patients showed decreased or absent filling of the cortical arteries. He concluded that this was due to reduction in the lumens of the vessels and therefore to the presence of cortical ischemia. Thus the site of vascular pathology is important when considering the possibility for operative cure.

(d) Renal Biopsy

In a recent report Vertes, Gravel and Goldblatt[47] indicated that in the careful assessment of some cases of renovascular hypertension by clearances or arteriography, occult bilateral intrarenal disease, due especially to arteriolar neph-

rosclerosis, may escape recognition. These workers believe that preoperative renal biopsy will indicate when nephrectomy or corrective surgery may fail. It may be deleterious in patients with bilateral renal disease in whom functional inequality is compounded by a main renal artery stenosis; this combination may mimic only renal artery obstruction. Thus "unilateral" renal arterial disease may be merely an unequal development of bilateral obliterative extra- or intrarenal vascular disease. They report that of 52 patients 30 had evidence of intrarenal disease bilaterally, even though arteriography and split function tests indicated "unilateral" disease. We feel that the UWT is an important adjunct in the assessment of each kidney separately. In addition, the UWT, if it had been done, might in these cases have shown bilateral positive results.

Renal biopsies should, therefore, be considered in bilateral positive cases to determine the intrarenal vascular pattern.

SUMMARY

An outline of the altered physiology produced by significant main renal artery stenosis has been presented. It forms the basis for an additional radiographic method in an attempt to diagnose both curable and incurable hypertension. The value of other radiographic investigations of the kidney is assessed and their limitations are described.

The urea washout modification of the rapid-sequence pyelogram embodies both an anatomical and physiological approach in the roentgen diagnosis of curable renovascular hypertension.

The essential principle of the UWT is the enhancement of the relative differences between the hyperconcentration of contrast medium in the collecting systems of ischemic and normal kidneys. At specific time intervals during the test the hyperconcentration is due to a decrease in renal plasma flow in the ischemic kidney resulting in a concomitant decrease in the glomerular filtration rate. Excessive sodium is reabsorbed with a resultant increased absorption of water due to the slow flow of filtrate through each tubule. The physical hemodynamic changes that produce this sequence of events are in all probability related to those that initiate the renin-angiotensin system and the subsequent hypertension. This paper has shown that there is a direct similarity on a functional basis. Diatrizoates (Hypaque*) and iothalamates (Conray†) are excreted by the glomeruli in an identical fashion to inulin and are not reabsorbed by the tubules.

Of the 146 hypertensive patients examined there were 26 (17.8%) positive UWTs in which there was direct confirmation of main renal artery stenoses by selective renal arteriography. Seven of these 26

*Hypaque—Winthrop.
†Conray—Mallinckrodt.

cases were confirmed bilateral positive results. An additional 16 positive findings did not have confirmatory arteriography. In addition, 12 of 13 "positive" tests with arteriography could be ascribed to conditions other than significant stenosis of a major arterial branch. A total of 55 cases were assessed therefore as having positive UWTs.

Eighteen of the 91 negative UWTs underwent selective renal arteriography. All of these 18 vascular studies were normal.

The UWT is shown to be valuable in the postoperative assessment after the operative repair of the renal artery defect. The demonstration of a physiological abnormality of diffuse intrarenal vascular disease by the UWT is reported in two cases, one patient with systemic lupus erythematosus and one with toxemia of pregnancy.

Decrease in renal size is not a feature of the majority of positive urea washout tests in patients with renal artery stenosis, and no significant disparity is noted in the relative change of length of the affected kidney after the start of the infusion. The rare case of an unrecognized segmental artery stenosis sufficient to produce hypertension may escape notice.

This prospective study of renovascular hypertension by the urea washout test, utilizing it as a *screening* test, has shown it to be of considerable value. The UWT demonstrates an acceptable degree of accuracy in the diagnosis of significant unilateral or bilateral main renal artery stenosis, whereas the simple intravenous urogram and the rapid-sequence urogram are considered by the authors to be of less value. Intrarenal diffuse small artery disease is also detectable by the urea washout test. Its value in segmental arterial disease is not as apparent. The urea washout test is not intended to supplant the arteriogram or the split function tests, but we feel that it is a simple, relatively inexpensive and more comprehensive screening test in experienced hands. Furthermore, it necessitates no special x-ray equipment, but rather an intelligent, experienced appraisal and evaluation.

A patient with a signficant stenosis of a main renal artery screened by the urea washout test, further assessed by arteriography, split function tests and possibly renal biopsy as well as a renal scan, should then be seriously considered for a curative operation.

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